# Epitomes

## Important Advances in Clinical Medicine

# Nuclear Medicine

*The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in nuclear medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association, and the summaries were prepared under its direction.*

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## Use of Thallium 201 in Tumor Evaluation

THALLOUS CHLORIDE Tl 201 is a safe, nontoxic radiopharmaceutical currently used to assess myocardial perfusion and viability. Its use has been increasing recently to detect tumors and to characterize tumor viability. This agent has been reported as being highly successful in the evaluation of brain tumors, thyroid cancer, parathyroid adenoma and carcinoma, carcinoma of the breast, primary bone tumors, soft tissue sarcomas, lymphoma, and several other tumor types.

The mechanism of $^{201}$Tl uptake in tumors appears to be related to its physical similarity to potassium. It has been demonstrated that the sodium-potassium-adenosine triphosphatase membrane transport system as well as a chloride-dependent cotransport mechanism, also within the cell membrane, are the two main mechanisms of transporting thallium into the tumor cell.

Because $^{201}$Tl entry into the tumor cell is dependent on active transport functions requiring intact energy-generating systems, viability studies can be done using this agent. These studies have shown thallium to be an excellent marker of viability. The success of tumor therapy can be determined by measuring the change in $^{201}$Tl tumor levels following a baseline evaluation. An increase in thallium activity after therapy indicates therapeutic failure, and a reduction in thallium activity within a tumor appears to be proportional to the success of the therapeutic regimen.

Thallous chloride Tl 201 has also been used successfully in differentiating malignant from benign disorders. Most hilar or mediastinal masses within the chest that are malignant will take up substantial amounts of $^{201}$Tl, but sarcoidosis appears to take up little, if any. In addition, malignant neoplasms of the breast have been shown to take up $^{201}$Tl, with sensitivities approaching 96% for palpable lesions. In contrast, fibrocystic changes, which may also cause palpable breast masses, show no $^{201}$Tl uptake. The use of $^{201}$Tl-thallous chloride has also been successful in differentiating certain benign bone abnormalities from malignancy. A variety of tumors are particularly suited for thallium examination, including osteogenic sarcomas, Ewing's sarcoma, and malignant fibrous histiocytoma.

Thallium imaging can be started immediately after administration and the study completed in one hour. The safety of the study has been demonstrated with no serious side effects. Radiation exposure is minimal. A disadvantage associated with thallium imaging is unpredictable gastrointestinal excretion that does not allow an accurate evaluation of the abdominal area. The brain, neck, chest, axilla, breast, and inguinal areas as well as skeletal system can be easily and accurately evaluated.

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## Technetium 99m-Hexamethyl Propyleneamine Oxime–Labeled Leukocytes for Diagnosis of Infection

INDIUM 111 ($^{111}$In) has been the primary radioisotope used to label leukocytes for detecting abscesses. Technetium 99m ($^{99m}$Tc), the most commonly used radioisotope in nuclear medicine, has a number of important advantages over $^{111}$In. Until recently, however, there have not been effective methods for labeling leukocytes with $^{99m}$Tc.

Technetium 99m-hexamethyl propyleneamine oxime ([$^{99m}$Tc]HMPAO) is a new radiopharmaceutical agent commonly used in brain imaging as a marker of cerebral blood flow. The complex is small, neutral, and lipophilic, allowing it to readily cross the intact blood-brain barrier. These same characteristics enable it to be used to label leukocytes. When incubated with leukocytes, the lipophilic $^{99m}$Tc complex crosses the plasma membrane and changes into a more hydrophilic complex that is trapped in the cell.

In vitro and in vivo studies of leukocyte chemotaxis and function following labeling with [$^{99m}$Tc]HMPAO have found no evidence of cellular damage. Comparisons of [$^{99m}$Tc]HMPAO-labeled cells with $^{111}$In-labeled leukocytes and the use of gallium citrate Ga 67 in infected patients indicate that $^{99m}$Tc-labeled leukocytes are equal, and in many cases superior, to the standard radiopharmaceuticals. Sensi-

tivities as high as 92% to 100% have been found. The comparison studies are especially convincing because the same patient's leukocytes can be labeled with both $^{111}$In-tropolone and [$^{99m}$Tc]HMPAO and then imaged simultaneously using different energy windows.

The most exciting advantage of [$^{99m}$Tc]HMPAO-labeled leukocytes over other labels is their ability to detect sites of infection within 30 minutes of administration. Leukocytes labeled with indium In 111 oxyquinolone detect as few as a third of cases of infections when imaged in the first 4 hours after administration; 24-hour delays are common (although some studies with $^{111}$In-oxine– and $^{111}$In-tropolone–labeled cells have shown a high sensitivity for infection in the first few hours after injection). The much more rapid diagnosis with [$^{99m}$Tc]HMPAO allows antibiotic or surgical therapy to be instituted earlier.

Leukocytes labeled with [$^{99m}$Tc]HMPAO have a number of other advantages as well. Unlike $^{111}$In-oxine, HMPAO labeling can be done in plasma, which enhances cell viability and prevents leukocyte activation. Technetium HMPAO is a more specific granulocyte label than $^{111}$In-oxine; in addition, the tag is eluted primarily from monocytes, resulting in a nearly pure granulocyte label without the need to do complicated separation techniques such as density gradient centrifugation.

Compounds containing $^{99m}$Tc provide better images than those containing $^{111}$In or gallium 67 because its energy is ideal for today's gamma cameras. The radiation exposure to the patient is reduced by a third to a half compared with $^{111}$In-labeled cells. Technetium is always available because it is obtained from generators on site rather than being shipped in. Finally, $^{99m}$Tc is considerably less expensive than the other commonly used radioisotopes.

There are some problems with [$^{99m}$Tc]HMPAO-labeled leukocytes, however. Bowel, biliary, and genitourinary excretion occurs. Because bowel activity does not appear until four hours after administration, early imaging will usually prevent false-positive diagnoses. Indium 111–labeled leukocytes, however, are not normally excreted into the bowel and therefore have an advantage in imaging abdominal and pelvic infections. Also, chronic infections in which leukocyte exchange is slowed may not be seen as well with [$^{99m}$Tc]HMPAO-leukocytes, as delays of 4 to 24 hours between administration and imaging may be required. Lower uptakes of [$^{99m}$Tc]HMPAO-granulocytes compared with $^{111}$In-labeled leukocytes are seen in experimentally induced abscesses at 18 hours after administration due to elution of the [$^{99m}$Tc]HMPAO label with time. Finally, [$^{99m}$Tc]HMPAO labeling of leukocytes for infection imaging is not currently approved by the US Food and Drug Administration and therefore may not be available at all sites.

In summary, [$^{99m}$Tc]HMPAO-leukocytes are an important new technique for imaging acute infection. For more chronic infections, in suspected infection of organ systems that normally excrete [$^{99m}$Tc]HMPAO, or in cases where a rapid answer is not needed, $^{111}$In-leukocytes or $^{67}$Ga-gallium citrate may be better choices.

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## Radionuclide Evaluation of Brain Death

SUCCESSFUL TRANSPLANTATION OF cadaveric organs requires the removal of organs soon after the donor's death. A prompt determination of the donor's death is necessary to avoid deterioration of the organs to be transplanted. How can it be determined when or if a critically injured, deeply comatose person on life support has died?

Since a landmark publication in 1968 by the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, there have been several revisions of the criteria. The currently most widely accepted criteria were established in a report to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. These "Guidelines for the Determination of Death" state that a person with irreversible cessation of circulatory and respiratory function is dead and that a person with irreversible cessation of all functions of the entire brain, including the brain stem, is dead.

In the case of a comatose person who is mechanically ventilated, the first criterion does not apply. When the patient is determined to be neurologically dead, death can be confirmed by showing absent brain blood flow. Absent blood flow to the brain is incompatible with life. As brain tissue dies, it swells. Intracranial pressure increases, resulting in a progressive reduction of circulation to the brain. When the intracranial pressure reaches systolic pressure, circulation ceases.

A lack of brain blood flow is well shown by four-vessel contrast angiography, which is accepted as legal proof of brain death in Germany and the Scandinavian countries. Alternative methods of brain death confirmation include digital subtraction angiography and dynamic computed tomography. All of these methods require transport of the person to the imaging area.

Radionuclide cerebral angiography using diethylenetriaminepentaacetic acid (DTPA) labeled with technetium 99m has been shown to be as accurate as contrast angiography in confirming brain death. The method is noninvasive and relatively inexpensive, and, most important, it can be done at the bedside using a portable gamma camera and computer. It is quick and easy to do. Radionuclide cerebral angiography has two disadvantages. A good intravenous bolus is essential. A poor bolus or equipment malfunction during the flow study may make the study uninterpretable, in which case it would need to be repeated. Also, radionuclide cerebral angiography demonstrates the presence or absence of cerebral blood flow and does not evaluate blood flow to the cerebellum, midbrain, or medulla. Therefore, it does not meet the strict criterion of the total absence of brain blood flow.

Technetium 99m-hexamethyl propyleneamine oxime (HMPAO) is a new lipophilic agent used for cerebral perfusion imaging. It is taken up by grey and white matter in proportion to blood flow (4:1). Normally the cerebellum is visualized. Therefore, the agent can answer the question, Is there subtentorial blood flow? Imaging is not dependent on a good intravenous bolus and is not subject to fluctuations in a hospital's electrical supply. If an image is lost because of, for example, an electrical surge, it can be repeated immediately with no significant delay. Disadvantages are the relatively high cost of an HMPAO kit and its instability after preparation: The tracer should be injected within 30 minutes of